MALNUTRITION AND IMMUNITY - A BRIEF REVIEW AND PRELIMINARY RESULTS*

F. B. Bang and B. G. Bang@

to a myriad of viruses and have major defects in immunity may be visualized as the consequence of three factors (Fig. 1) yet which must be considered separately; t.**

Immunology is the most rapidly developing field involved in the interaction, and a diagram of present understanding of the sequence of events in the immune system (Fig. 2) may serve to clarify discussion. Some relations between the three important cell types in immune response are indicated: the T lymphocyte, the B lymphocyte, and the macrophage. Detailed sequential studies of labelled cells, and of cell replacement after lethal irradiation¹ have identified the bone marrow as the source of all three cell types.

@ The Johns Hopkins University, Center for Medical Research, Calcutta, India
Paper presented at sixth All Nepal Medical conference.

* The tests which provided the preliminary data on the T and B cells represent current work at the Institute of Child Health in collaboration with Dr. K. L. Mukherjee and Dr. D. Mahalanabis. In a related program, Dr. D. Sinha is studying the relationship of Vitamin A deficiency to infection in Jhalda in Western West Bengal.

** Recognizing this, the WHO has published protocols for the study of immune mechanisms in different areas of the world, since both in different areas of the world, since both infections and diets vary locally. We are happy to be part of this comparative program.

Fig. 1.

The diagram shows that a lymphocyte derived from bone marrow may develop into either of two functional cell types. It may pass through the thymus where it acquires the capacity for direct action against antigen and can thence-forward function in cell-mediated immune responses. This is a "T" cell. Or a stem lymphocyte may pass through a specialized lymphoid organ system associated with the gut: the Bursa of Fabricius in the case of birds, a functionally equivalent—probably diffused—system in mammals, where it acquires the capacity to synthesize particular immunoglobulins. This is a "B" cell.

Macrophages, also derived from the bone marrow, may home to lymphoid nodules and spread out to form a network of processes which have the capacity to trap and hold antigens. T and B cells may enter such a nodule, with antigenic stimulus they may interact in such a way that the T cells are stimulated to reproduce rapidly so that the nodule increases greatly in size and forms an active "germinal center" for production of antigen-

reactive cells. Antigen-reactive T cells may thus either circulate through the body and engage antigens at particular sites, or may act locally on trapped antigens. B cells may assist in the response to trapped antigens or may circulate and produce humoral immunoglobulins.

Fig. 2.

The T cell is the lymphocyte responsible for cell-mediated immune responses such as graft-versus-host response, response to invading tumors, to virus-infected cells, and to tubercle bacilli. Until recently there was no method by which T cells could be studied in vitro because pure preparations of lymphocytes could not be obtained. One of the methods now used to obtain nearly pure lymphocytes is to pass freshly drawn blood through a methylcellulose-isopaque gradient⁸ of a specific density which allows most blood cells other than lymphocytes to sediment through the gradient so that a quite pure layer of lymphocytes remains resting on the surface of the gradient. We are currently using this method to obtain preparations of lymphocytes.

we will emphasize cell-mediated immune responses in the discussion which follows, primarily because current data on the effect of nutrition on serological immunity are unclear and inconclusive.

The anatomy of the immune system is becoming clearer, and earlier clues can be placed in perspective. Thymic atrophy in starvation has long been recognized. For example as early as 1937 Vint⁹ showed that children with kwashiorkor had atrophic thymuses. We be-

ame interested in the three-compartment interaction during studies of virus-infected malnourished chickens, for we found that the combination of vitamin A deficiency and a myxovirus infection had a remarkable effect on lymphoid tissues.⁴ The combination was catastrophic in that both the thymus and the bursa were depleted of lymphocytes from the critical cortical areas of the respective organs. The vitamin deficiency alone or the infection alone had only moderate effects.

This effect was reminiscent of the fact that children with kwashiorkor fail to respond to live yellow fever vaccine⁵. Also, it was shown 60 years ago that children with measles had depressed tuberculin responses, and more recently Harland showed that in Uganda kwashiorkor itself suppressed the tuberculin reaction⁶. The tuberculin reaction is now known to be a primary manifestation of cell-mediated immunity. Uganda incidentally is one of the African areas (Nigeria is another) where the unholy alliance of measles and kwashiorkor causes 100 times more child mortality than does measles in the normally nourished⁷. In the case of measles-kwashiorkor, a child is the victim of the double effect of each factor on the cell-mediated immune response.

In this connection recent studies on tumor immunity have shown that those patients who can become sensitized to the rare chemical compound dinitrochlorobenzene (DNCB) are better able to combat their own tumor cells than patients who fail to become sensitized⁸. With our associations we have used the DNCB skin test to study responses in malnourished adults (Table 1) and infants (Table 2) and results indicate that refeeding usually, but not always, restores the normal capacity of T cells to mount a delayed immune response to a new antigen. Similar results have been recently published from Thailand⁹. Thus the population of T cells available to the malnourished individual apparently cannot recognize a new antigen.

Perhaps the most important single paper in the recent literature on the cell-mediated immune (c.m.i.) response is that of Smythe and his colleagues in South Africa¹⁰. With combined clinical, anatomical and laboratory methods they showed that children with protein-calorie malnutrition have defective c.m.i. responses related primarily to the T cell system. We are attempting to apply one of the recently developed immunologic methods of measuring T and B cell responses in malnourished infants from the time of hospital admission through refeeding. The antigen-reactive T lymphocyte population in circulating human blood can be measured by determining the percentage of purified washed lymphocytes which will absorb sheep erythrocytes into their surfaces, forming an aggregation around the lymphocyte which, in the microscope, simulates a "rosette". This is a T cell rosette. B cells are identified in a similar way by using sheep erythrocytes treated by antibody and complement in amounts which do not hemolyze the erythrocytes.¹

Results

Our studies at the Institute of Child Health are quite preliminary. One infant with kwashiorkor had very low T and B cell responses which both improved markedly after several

weeks' refeeding but were low again after her second sensitization with DNCB (Fig. 3). Combined records of 6 children admitted with kwashiorkor or marasmus indicate thus far that kwashiorkor depresses both T and B cells while marasmus does not. Obviously an extensive group of children must be studied before relative data are established. But such data will not be uncomplicated. For example, as we study normal adults we find that the proportion of their T cells decreases sharply during acute respiratory infection. Assuming that this is also true in children, the multitude of viruses that infect infants in the crowded living conditions in developing areas of the world may participate in the story of kwashiorkor.

Results of tests for T and B cell rosetting values in a body with kwashiorkor. Tests were at 2 week intervals. By the 6th week T cell values rose, were maintained for a month. A 2nd sensitizing dose of DNCB (S_2) was given a week before the next test, when a low rosetting value resulted. White bars-T cells; black bars-B cells.

In summary, it may be said that the interactions of the components diagrammed in Fig. 1 are apparent in three situations in our study so far : (1) the malnourished child is exposed to a myriad of viral agents, (2) there is a clear synergistic effect between malnutrition and infection on the immune system in experimental models, and (3) there is T cell depression in children with kwashiorkor, and in normal adults during acute respiratory infection. The interaction of nutrition and virus infection on the immune system needs continued study in the laboratory and in human populations, especially in infants.

TABLE I.
ADULTS (SMITH)

Before Therapy					After		
S ¹		C ¹	C ²		S ²		C ³
*	8 d	+	+	12 wk	+		
*	12 d	+		7 wk	++		
*	14 d	0		7 wk	0	*	2 wk +++
*	13 d	0		7 wk	0	*	2 wk ++
*	14 d	±		6 wk	0	*	2 wk +++
*	14 d	+					

Of 6 adults 3 were sensitized with DNCB (S₁). Of these 6 three failed to respond to challenge doses (C¹ and C²) before refeeding. After refeeding and following a second sensitizing (S²) dose all three gave positive response to the 3rd challenge (C³).

TABLE 2
INFANTS (MAHALANABIS)

No.	S ₁	T ₁	S ₂	T ₂	T ₃	T ₄
1 (K)		0		0	0	0
5 (M)		0	+	++		
6 (K)		0	+++	0	0	
8 (K)		0		0		

All 4 malnourished infants sensitized with DNCB before refeeding (S₁) and challenged soon after (T₁) all failed to respond. After a second sensitizing a single marasmic infant had positive response to the sensitizing and subsequent test doses. None of the 3 kwashiorkor children responded positively to 2nd, 3rd or 4th challenges (T₂, T₃, T₄) including one who was sensitized a second time (S₂).

References:

1. Humphrey, J. H. and R. G. White. 1970. *Immunology for Students of Medicine*, Ch. 7. Blackwell, Oxford.
2. Jondal, M., G. Holm, H. Wigzell, 1972. Surface Markers on Human T and B Lymphocytes. *J. Exp. Med.* 136: 207-215.
3. Vint, F. W. 1937. Post-mortem Findings in Natives of Kenya. *E. Afr. Med. J.* 13: 332-340.
4. Bang, B. G. and F. B. Bang. 1972. Lymphocyte Depression Induced in Chickens. *Am. J. Pathol.* 68: 147-158.
5. Brown, R. E. and M. Katz. 1966. Failure of Antibody Production to Yellow Fever Vaccine in Children with Kwashiorkor. *Trop. geogr. Med.*, 18: 125-128.
6. Harland, P. S. E. G. 1965. Tuberculin Reactions in Malnourished Children. *Lancet*, 719.
7. Morley, D. C., M. Woodland, and J. W. Martin. 1963. Measles in Nigerian Children. *J. Hyg. Cambridge*, 61: 115-134.
8. Edelman, R., R. Suskind and R. E. Olson. 1973, Mechanisms of Defective Delayed Cutaneous Hypersensitivity in Children with Protein-Calorie Malnutrition. *Lancet*, March, 506-508.
9. International Symposium on Protein-Calorie Malnutrition, Chiang Mai, Thailand, January 1973.
10. Smythe, P. M., M. Schonland, C. G. Brereton-Stiles, H. M. Coovadia, H. G. Grace, W. E. K. Loening, A. Mafoyane, M. A. Parent and G. H. Vos. 1971. Thymolymphatic Deficiency and Depression of Cell-mediated Immunity in Protein-Calorie Malnutrition. *Lancet*, 939-943.
11. Faulk, P. W., 1971. Some Effects of Malnutrition on the Immune Responses, *Wld Hlth Org.*